IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

DECLARATION OF MARY B. MATTERER IN SUPPORT OF DEFENDANT IMPAX LABORATORIES, INC.'S MOTION TO COMPEL DEPOSITION PURSUANT TO FED. R. CIV. P. 30(b)(6)

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Attorneys for Defendant
IMPAX LABORATORIES, INC.

Dated: March 16, 2007
Redacted Date: March 23, 2007

I, Mary B. Matterer, declare:

1. I am an attorney at the law firm of Morris James, LLP, counsel of record for Defendant Impax Laboratories, Inc. ("Impax") in the above-referenced case. I have personal knowledge of the facts set forth in this declaration.

2. I submit this Declaration in support of Defendant Impax's Motion to Compel Deposition Pursuant to Fed. R. Civ. P. (30)(b)(6).

3. A true and correct copy of a March 9, 2007 letter from Daniel Kassabian, counsel to Impax, to Basil Lewris and Linda Wadler, counsel to Wyeth, is attached hereto as Exhibit A.

4. A true and correct copy of Impax Laboratories, Inc.'s Second Amended Notice of Deposition Pursuant to Rule 30(b)(6) is attached hereto as Exhibit B.

5. A true and correct copy of a transcript from the March 2, 2007 in this action before the Honorable Joseph J. Farnan, Jr. is attached hereto as Exhibit C.

6. A true and correct copy of a March 13, 2007 letter from Barbara Rudolph, counsel to Wyeth, to Daniel Kassabian, counsel to Impax, is attached hereto as Exhibit D.

7. A true and correct copy of Wyeth's Supplemental Responses to Defendant Impax's Interrogatory Nos. 5, 7, 9, 12, 17 and 19 dated October 10, 2006 is attached hereto as Exhibit E.

8. A true and correct copy of Wyeth's Supplemental Responses to Defendant Impax's Interrogatory Nos. 5, 6, 10, 11, 13, 17, 18, 19, 26 and 27 dated January 12, 2007 is attached hereto as Exhibit F.

9. A true and correct copy of the Markman Opinion dated September 6, 2005 in Civil Action No. 03-1293, In the United States District Court for the District of New Jersey, styled *Wyeth v. Teva Pharmaceuticals USA, Inc.,* is attached hereto as Exhibit G.

10. A true and correct copy of U.S. Patent No. 4,138,475 is attached hereto as Exhibit H.

11. A true and correct copy of an Office Action mailed January 4, 2001 in United States Patent Application Ser. No. 09/488,629 is attached hereto as Exhibit I.

12. A true and correct copy of U.S. Patent No. 6,274,171 is attached hereto as Exhibit J.

13. A true and correct copy of an excerpt of the transcript of Richard DeNeale dated December 22 and 23, 2004 in Civil Action No. 03-1293, in the United States District Court for the District of New Jersey, styled *Wyeth v. Teva Pharmaceuticals USA, Inc.,* is attached hereto as Exhibit K.

14. A true and correct copy of an excerpt of the transcript of Stephen White dated October 8, 2004 in Civil Action No. 03-1293, in the United States District Court for the District of New Jersey, styled *Wyeth v. Teva Pharmaceuticals USA, Inc.,* is attached hereto as Exhibit L.

15. A true and correct copy of an excerpt of the transcript of John Lamer dated October 14, 2004 in Civil Action No. 03-1293, in the United States District Court for the District of New Jersey, styled *Wyeth v. Teva Pharmaceuticals USA, Inc.,* is attached hereto as Exhibit M.

16. A true and correct copy of an excerpt of the transcript of John Clark dated November 4, 2004 in Civil Action No. 03-1293, in the United States District Court for the District of New Jersey, styled *Wyeth v. Teva Pharmaceuticals USA, Inc.,* is attached hereto as Exhibit N.

17. A true and correct copy of an excerpt of the transcript of Deborah Sherman dated October 20, 2004 in Civil Action No. 03-1293, in the United States District Court for the District of New Jersey, styled *Wyeth v. Teva Pharmaceuticals USA, Inc.,* is attached hereto as Exhibit O.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed at Wilmington, Delaware on March 16, 2007.

MARY B. MATTERER (I.D. NO. 2696)

EXHIBIT A

HellerEhrman LLP

March 9, 2007

Via E-mail & U.S. Mail

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Re: ***Wyeth v. Impax Laboratories, Inc.***
U.S. District Court, District of Delaware, Civil Action No. 06-222 JJF

Dear Counsel:

Please find enclosed Impax's Second Amended Notice Of Deposition Of Wyeth Pursuant To Fed. R. Civ. P. 30(b)(6). We have substantially narrowed the Notice and reorganized it under major headings to fully comply with the Court's statements.

We should be able to get through these topics in four (4) days of depositions running from 9:00 a.m. to 1:00 p.m. and 2:00 p.m. to 5:00 p.m.

This assumes that there is adequate preparation of the deponent(s), objections are stated concisely and in a non-argumentative manner, the witnesses are instructed not to answer only when necessary to preserve a privilege, that there is no impediment, delay or other conduct that frustrates the fair examination of the deponent(s) (*See* Fed. R. Civ. P. 30(d)(1) & (3)) and that we are given ten (10) days notice of the witnesses which will testify about each topic and when that topic will be addressed.

Based on the information we have to date, we estimate the time-frame being broken down among the below eight (8) general topics as follows:

I. WYETH'S ALLEGED CONCEPTION AND REDUCTION TO PRACTICE OF THE "INVENTIONS" IN THE PATENTS (3 hours)

II. EVOLUTION OF WYETH'S COMMERCIAL PRODUCT -- DEVELOPMENT AND CHARACTERISTICS (4 hours)

III. WYETH'S FAILURES OF OTHER EXTENDED RELEASE TECHNOLOGIES WITH VENLAFAXINE (4 hours)

IV. OTHER EXTENDED RELEASE FORMULATIONS WHICH MIGHT INVALIDATE THE WYETH PATENTS OR RENDER THEM UNENFORCEABLE (4 hours)

V. FACTS EVIDENCING INEQUITABLE CONDUCT BY MISCHARACTERIZING THE CLINICAL STUDIES ON NAUSEA AND FAILURE TO DISCLOSE HIGHLY MATERIAL INFORMATION (3 hours)

VI. FACTS SUPPORTING STATEMENTS IN THE PATENTS OR REQUIRED TO UNDERSTAND THEM; AND PATENT PROSECUTION PRACTICE AND RECORDKEEPING (3 hours)

VII. WYETH'S NEW DRUG APPLICATION (NDA) AND STATEMENTS MADE TO THE FDA THAT CONTRADICT THE PATENTS AND WYETH'S INTERPRETATION OF THE CLAIMS (3 hours)

VIII. THE ALLEGED COMMERCIAL SUCCESS BY WYETH IS NOT ATTRIBUTABLE TO THE ALLEGED INVENTION BUT TO ADVERTISING AND PROMOTION (4 hours)

Obviously, some topics may require less time and some more. So the above estimate should not be considered a restriction as to the amount of time actually spent on any one topic or even groups of topics, because a deponent may provide testimony that requires additional time to explore a given topic or group of topics or may dispose of another topic quickly. But the overall length should not go over four days.

You should also note that beyond reorganizing some topics, many have been reduced in scope and/or the subject matter has been set forth with additional particularity, and some have been eliminated completely. Despite this, in a further effort to move forward with this deposition in an expeditious manner, we have voluntarily provided more information about the subject matter of these topics beyond the "reasonable particularity" called for by Rule 30(b)(6) and the case law interpreting it. Of course, we will require the same of Wyeth if and when it seeks a Rule 30(b)(6) deposition of Impax.

Accordingly, we believe this notice is well within the scope of reasonable discovery for a patent infringement case with three patents-at-issue, Wyeth's assertion of facts dating back to the early 1990's, and with the range of issues currently in dispute. *Cf. AMP, Inc. v. Fujitsu Microelec., Inc.*, 853 F. Supp. 808, 831 (M.D. Pa. 1994) (requiring deposition of defendant and accused patent infringer represented by Finnegan Henderson on 25 topics

noticed pursuant to Rule 30(b)(6), and rejecting contention that facts alleged in support of defendant's allegations and denials were outside of its control). In light of this, the notice is not unduly burdensome in view of the factors set forth in Rule 26(b)(2)(C)(iii). *Cf. Dynacore Holdings Corp. v. U.S. Philips Corp.*, No. 01-CIV-5012, 2002 WL 31233246, *5 (S.D.N.Y. Oct. 4, 2002) (rejecting assertion by defendants represented by Finnegan Henderson that the Rule 30(b)(6) deposition would be unduly burdensome without specific facts regarding factors in Rule 26(b)(2)(C)(iii)).

If Wyeth still refuses to produce any witness pursuant to this notice, please let us know the reasons for its refusal immediately. To the extent Wyeth raises an issue with a particular topic or a group of topics, we again request that the deposition move forward as to the other groups of topics noticed because there is no need to further delay as to those undisputed topics. In the event that the parties cannot come to an agreement by or before March 16, 2007, Impax will file a motion on that day to compel this deposition that will be heard on or before April 13, 2007. Obviously, we hope to avoid needless motion practice, especially given that the parties have previously briefed the issues and the above addresses additional concerns raised by the Court.

We look forward to your prompt reply.

Best regards,

D. Kassabian

Daniel N. Kassabian

Enclosure

cc: M. Patricia Thayer, Esq.
John M. Benassi, Esq.
Jessica R. Wolff, Esq.
Samuel F. Ernst, Esq.
Mary B. Matterer, Esq.
Jack B. Blumenfeld, Esq.
Karen Jacobs Louden, Esq.

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	)	Civil Action No.: 06-222 JJF

DEFENDANT IMPAX LABORATORIES, INC.'S SECOND AMENDED NOTICE OF DEPOSITION OF WYETH PURSUANT TO FED. R. CIV. P. 30(B)(6)

PLEASE TAKE NOTICE that commencing at 9:00 a.m. on April 3, 2007 at the offices of Finnegan Henderson Farabow Garrett & Dunner LLP, 901 New York Ave., N.W., Washington, D.C. 20001, or at another mutually agreed upon time and place, Defendant Impax Laboratories, Inc. ("Impax"), through its attorneys, will take the deposition of Plaintiff Wyeth pursuant to Federal Rule of Civil Procedure 30(b)(6). In advance of the deposition, Wyeth shall designate one or more of its directors, officers, managing agents, or other persons who will testify at the deposition on behalf of Wyeth as to all information known or reasonably available to Wyeth regarding the topics set forth in Schedule A hereto and the definitions in Schedule B. In addition, "(1) the deponent must be knowledgeable on the subject matter identified as the area of inquiry, (2) Wyeth must designate more than one deponent if necessary in order to respond to the relevant areas of inquiry specified by Impax, (3) Wyeth must prepare the witness to testify on matters not only known by the deponent, but those that should be known by Wyeth; and (4) Wyeth must substitute an appropriate deponent when it becomes apparent that the previous deponent is unable to respond to certain relevant

areas of inquiry." 7-30 MOORE'S FEDERAL PRACTICE - CIVIL §30.25 (2006) (quoting *Alexander v. FBI*, 186 F.R.D. 137, 141 (D.D.C. 1998)). The deposition will take place upon oral examination before a notary public or other person authorized to administer oaths, will be recorded by stenographic and/or sound and video means, and will continue from day to day until completed. You are invited to attend and participate.

Dated: March 9, 2007

M. PATRICIA THAYER (*pro hac vice*)
JOHN M. BENASSI (*pro hac vice*)
JESSICA R. WOLFF (*pro hac vice*)
DANIEL N. KASSABIAN (*pro hac vice*)
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IMPAX LABORATORIES, INC.

SCHEDULE A

DEPOSITION TOPICS

I. WYETH'S ALLEGED CONCEPTION AND REDUCTION TO PRACTICE OF THE ALLEGED "INVENTIONS" IN THE PATENTS

1. FACTS supporting or evidencing WYETH's conception and reduction to practice of the alleged invention(s) claimed in each of the asserted claims of the PATENTS IN SUIT and claim 1 of U.S. Patent No. 6,274,171 B1. (This should be interpreted to include the identity of documents and witnesses as well as when and where those conceptions and reductions to practice took place, who was present and/or participated, what transpired, what DOCUMENTS were authored contemporaneously or near contemporaneously to record what transpired, and the significance of conception and reduction to practice milestones.)

2. Non-privileged information, unless Wyeth knowingly waives privilege, regarding all invention records CONCERNING the asserted claims of the PATENTS IN SUIT and claim 1 of U.S. Patent No. 6,274,171 B1. (This includes without limitation when such records were authored, by whom, pursuant to whose instruction or pursuant to what policy (if any), to whom they were provided, how were they provided, when they were provided, what was the purpose of providing the invention records to such person(s), whether oral communications were contemporaneously or near contemporaneously made with the provision of the records, and where such records are usually kept in the ordinary course of business.)

II. EVOLUTION OF WYETH'S COMMERCIAL PRODUCT -- DEVELOPMENT AND CHARACTERISTICS

3. FACTS relating to the evolution of the composition and formulations of EFFEXOR XR and the development thereof from June 1990 through July 2002. (This should be interpreted to include modification to the formulations during that period, methods of manufacturing, when and where they were developed, who developed them, and what materials and methods were used to develop them). To limit this request further

we are acceding to Wyeth's request to not include toxicology, quality control, animal testing, purchasing and qualification of raw materials, or packaging.

4. FACTS relating to the *in vitro* and *in vivo* release and bioavailability profiles of EFFEXOR XR from June 1990 through July 2002, including target profiles, when and where those profiles were first achieved, who was involved and oversaw this achievement, and what materials and methods were used to test and achieve them, modifications to those release profiles, and difficulties in consistently replicating those profiles. (EFFEXOR XR should be interpreted to include formulations prepared in the development of WYETH'S commercial EFFEXOR XR™, but excluding hydrogel tablets and gelucire capsules.)

III. WYETH'S FAILURES OF OTHER EXTENDED RELEASE TECHNOLOGIES WITH VENLAFAXINE

A. Hydrogel Tablets

5. The composition of EXTENDED RELEASE FORMULATIONS by WYETH comprising VENLAFAXINE in *hydrogel tablets*, and its development history from June 1990 through March 1996. (These should be interpreted to include modification to the formulations during that period, methods of manufacturing, when and where those formulations were developed, who developed them, and what materials and methods were used to develop them.) To limit the request further and acceding to Wyeth's request, this does not include toxicology, quality control, animal testing, purchasing and qualification of raw materials, or packaging.

6. FACTS relating to the *in vitro* and/or *in vivo* release profiles of EXTENDED RELEASE FORMULATIONS by WYETH comprising VENLAFAXINE in *hydrogel tablets*, from June 1990 through March 1996. (These should be interpreted to include target profiles, when those profiles were first achieved, who was involved and oversaw this achievement, what materials and methods were used to test and achieve

them, modifications to those release profiles, and difficulties in consistently replicating those profiles.)

B. Gelucire Tablets

7. FACTS relating to the composition of EXTENDED RELEASE FORMULATIONS by WYETH comprising VENLAFAXINE in *Gelucire capsules*, and the development thereof from June 1990 through March 1996. (These should be interpreted to include modification to the formulations during that period, methods of manufacturing, when and where those formulations were developed, where they were developed, who developed them, and what materials and methods were used to develop them.) To limit the request further and according to WYETH's request this does not include toxicology, quality control, animal testing, purchasing and qualification of raw materials, or packaging.

8. FACTS relating to the *in vitro* and/or *in vivo* release profiles of an EXTENDED RELEASE FORMULATIONs by WYETH comprising VENLAFAXINE and Gelucire capsules, from June 1990 through March 1996. (These should be interpreted to include target profiles, when those profiles were first achieved, where they were they achieved, who was involved and oversaw this achievement, what materials and methods were used to test and achieve them, modifications to those release profiles, and difficulties in consistently replicating those profiles.)

IV. OTHER EXTENDED RELEASE FORMULATIONS WHICH MIGHT INVALIDATE THE WYETH PATENTS OR RENDER THEM UNENFORCEABLE

A. Alza Art

9. FACTS relating to the composition and intended use of EXTENDED RELEASE FORMULATIONS comprising VENLAFAXINE utilizing ALZA's OROS® oral delivery technology, and the historical development thereof from June 1990 through July 2002. (These should be interpreted to include the formulations' intended use by patients, whether the formulations were expected to provide a therapeutic blood plasma

concentration of VENLAFAXINE over a twenty four hour period with diminished incidences of nausea and emesis, whether the formulations were expected to eliminate the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of VENLAFAXINE, modification to the formulations during that period, methods of manufacturing, when those formulations were developed, where they were developed, who developed them, and what materials and methods were used to develop them). To limit this request further we are acceding to Wyeth's request to not include toxicology, quality control, animal testing, purchasing and qualification of raw materials, or packaging.

10. FACTS relating to the *in vitro* and/or *in vivo* release profiles of an EXTENDED RELEASE FORMULATION by WYETH comprising VENLAFAXINE and utilizing ALZA's OROS® oral delivery technology, from June 1990 through July 2002, including target profiles, when those profiles were first achieved, where they were they achieved, who was involved and oversaw this achievement, what materials and methods were used to test and achieve them, modifications to those release profiles, and difficulties in consistently replicating those profiles.

B. Propranolol and Other Prior Art

11. WYETH's knowledge of the comparison of the solubility of Propranolol to VENLAFAXINE, studies, tests, trials, research, or experiments conducted from June 1990 through July 2002, that compare chemical properties, including without limitation solubility, of propranolol and its salts, with that of VENLAFAXINE and its salts.

V. FACTS EVIDENCING INEQUITABLE CONDUCT BY MISCHARACTERIZING THE CLINICAL STUDIES ON NAUSEA AND FAILURE TO DISCLOSE HIGHLY MATERIAL INFORMATION

12. FACTS showing that the NAMED INVENTORS and persons involved in the prosecution of the PATENTS IN SUIT, were aware of an article by Lynn A. Cunningham, M.D., entitled *Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients with Major Depression*, published in

volume 9, no. 3 of the Annals of Clinical Psychiatry in 1997 prior to and during the prosecution of the PATENTS IN SUIT.

13. The persons at WYETH involved in drafting, reviewing, editing, commenting on, or revising drafts of the article by Lynn A. Cunningham, M.D., entitled *Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients with Major Depression*, published in volume 9, no. 3 of the Annals of Clinical Psychiatry in 1997, including the titles of, job responsibilities of, and reporting structure surrounding those persons.

14. FACTS showing that NAMED INVENTORS and persons involved in the prosecution of the PATENTS IN SUIT, were aware of an article by Richard Entsuah, Ph.D et al, entitled *A Benefit Risk Analysis of Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients with Major Depression*, published in volume 33, no. 4 of the Psychopharmacology Bulletin in 1997 prior to and during the prosecution of the PATENTS IN SUIT.

15. The persons at WYETH involved in drafting, reviewing, editing, commenting on, or revising drafts of the article by Richard Entsuah, Ph.D et al, entitled *A Benefit Risk Analysis of Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients with Major Depression*, published in volume 33, no. 4 of the Psychopharmacology Bulletin in 1997, including the titles of, job responsibilities of, and reporting structure surrounding those persons.

16. FACTS evidencing WYETH's knowledge and research prior to July 2002 demonstrating or refuting that the EXTENDED RELEASE FORMULATION comprising VENLAFAXINE claimed in the PATENTS IN SUIT provided a therapeutic blood plasma concentration of VENLAFAXINE over a twenty-four hour period with diminished incidences of nausea and emesis.

17. FACTS evidencing WYETH's knowledge and research prior to July 2002 demonstrating or refuting that the EXTENDED RELEASE FORMULATION comprising

VENLAFAXINE claimed in the PATENTS IN SUIT eliminated the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of VENLAFAXINE.

VI. FACTS SUPPORTING STATEMENTS IN THE PATENTS OR REQUIRED TO UNDERSTAND THEM; AND PATENT PROSECUTION PRACTICE AND RECORDKEEPING

18. FACTS supporting examples 1 though 7 of the PATENTS IN SUIT, including without limitation the data and experimental records underlying Examples 1 though 7 and DOCUMENTS evidencing that data and experimental records.

19. FACTS supporting tables 1 though 3 of the PATENTS IN SUIT, including without limitation the data underlying Tables 1 through 3 and DOCUMENTS produced by WYETH evidencing that data.

20. The support for, the drafting of, the preparation of, and intended meaning of the following passage of the PATENTS IN SUIT:

> The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

21. The support for, the drafting of, the preparation of, and the intended meaning of the following passage of the PATENTS IN SUIT:

> It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble.

22. The support for, the drafting of, the preparation of, and intended meaning of the following passage from the Reply Under Rule 111 With Amendment Under

Rule 115 of November 5, 1997 filed with the PTO in U.S. Patent Application, serial no. 08/964,328:

> Moreover, there is a tremendous difference in water solubility of the two compounds. The water solubility of propanolol hydrochloride is 93 mg/ml, whereas that of venlafaxine hydrochloride is 574 mg/ml – i.e. 6 fold greater.

23. WYETH's practices and policies from June 1990 through July 2002 with respect to the prosecution of U.S. patent applications. (This includes the preparation of invention disclosures, evaluation of inventions, performing prior art searches, preparing patent applications, informing inventors of their duty of candor to the Patent Office, gathering and submitting prior art during the course of patent prosecution, evaluation of U.S. Patent and Trademark Office actions and examiner amendments, drafting and review of responses to Office actions, decisions to file provisional, continuation or continuation-in-part applications, and decisions to abandon applications.)

24. WYETH's procedures for collecting and maintaining DOCUMENTS and/or THINGS in their central files, archival or storage locations, and/or kept by individual employees. (This includes without limitation how the DOCUMENTS are organized in central files and/or archival or storage locations, the criteria for whose DOCUMENTS should be or were collected, and what measures are or were taken to ensure that all relevant documents are or were collected in response to requests for DOCUMENTS and THINGS propounded by IMPAX in this action and the defendants in *Wyeth v. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.*, Civil Action No. 03-CV-1293 (WJM) before the United States District Court for the District of New Jersey.)

25. FACTS and DOCUMENTS CONCERNING the affirmative statements and denials in paragraphs 67 and 68 of WYETH'S REPLY.

VII. WYETH'S NEW DRUG APPLICATION (NDA) AND STATEMENTS MADE TO THE FDA THAT CONTRADICT THE PATENTS AND WYETH'S INTERPRETATION OF THE CLAIMS

26. FACTS evidencing the following parts and contents of NDA No. 20-699 including without limitation any amendments thereto through July 2002:

(a) Integrated Safety Summary

(b) Summary of Human and Pharmacokinetics and Bioavailability

(c) The passage with respect to 600B-144FR stating that that there was "a dissociation between peak venlafaxine concentration and peak nausea. In all treatment conditions the maximum nauseating effect occurred before the time of peak concentration . . . . Compared with venlafaxine CF, the ER formulation, which reached comparable levels with a delayed tmax produced a much less intense maximum effect and a decrease of 63% in the area under the concentration-time curve (AUC) of nausea normalized by dose."

(d) The passage with respect to 600B-144FR stating that that there was "The incidence and severity of nausea would be expected to be less with venlafaxine ER than venlafaxine IR. This conclusion is based on the results of the study 600B-144FR...The incidence of nausea as an adverse event and the severity of nausea, measured as the AUC for a visual analog scale, where lower with venlafaxine ER administration than with venlafaxine IR administration."

VIII. THE ALLEGED COMMERCIAL SUCCESS BY WYETH IS NOT ATTRIBUTABLE TO THE ALLEGED INVENTION BUT TO ADVERTISING AND PROMOTION

A. Advertising, pricing and marketing

27. For the years 1997 through the second quarter of 2006, causes in any fluctuations of, and strategies to maintain or increase, the market share of EFFEXOR XR in the United States.

28. For the years 1997 through the second quarter of 2006, advertising budgets and the content and effectiveness of any advertising and promotional plans and

efforts for EFFEXOR XR in the United States, including without limitation detailing, sampling, and print, radio, and television advertisements, the size of the marketing and sales force, yearly advertising budgets and expenditures.

29. For the years December 2005 to the present, strategies to shift or switch the subscription and/or the consumption of EFFEXOR XR to desvenlafaxine succinate, to be marketed as Pristiq or as another brand name in the United States. (This includes any expected changes in market share of EFFEXOR XR, and any planned print, radio, and television advertisements, the preparation marketing force, rebates, discounts, or changes in pricing pursuant to such strategies.)

30. For the years 1994 through 1998, the content and effectiveness of any advertising and promotional efforts for EFFEXOR in the United States, including without limitation detailing, sampling, and print, radio, and television advertisements, the size of the marketing and sales force, yearly advertising budgets and expenditures.

31. All correspondence with its advertising agencies involved in advertising EFFEXOR and EFFEXOR XR.

B. Revenue, expenses and profitability

32. Revenue, expenses, and profitability for the years 1997 through the second quarter of 2006 from the sale of EFFEXOR XR in the United States, including without sales projections, actual sales, market shares, and profit margins;

SCHEDULE B

DEFINITIONS FOR DEPOSITION TOPICS

When used in the following deposition topics, the following definitions apply:

1. "WYETH" means Plaintiff Wyeth and that company as it was previously named and any related companies, parents, divisions, or subsidiaries, past or present, located in the U.S. or abroad, and the past or present directors, officers, employees, agents, representatives or attorneys thereof.

2. "IMPAX" means Defendant IMPAX Laboratories, Inc. and its past or present directors, officers, employees, agents, representatives or attorneys known to WYETH.

3. "CONCERNING" means referring to, relating to, regarding, comprising, constituting, containing, demonstrating, describing, discussing, evidencing, evincing, evidencing, indicating, on the subject of, on the topic of, showing, or prepared in connection with the stated matter.

4. "DATE" means the exact day, month, and year, if so ascertainable, or if not, the best approximation (including relationship to other events).

5. "DOCUMENT" or "DOCUMENTS" means all written, printed, typed, electronically produced, electronically stored, photostatic, photographed, recorded, or otherwise reproduced communications or records of every kind and description, whether comprised of letters, words, pictures, sounds, symbols, or combinations thereof. DOCUMENTS include originals as well as drafts, copies, marked-up copies, non-identical duplicates, and computer files, including backup or archival copies.

6. "THING" or "THINGS" means any tangible item, including without limitation models, prototypes, research models or samples, and samples of any device or apparatus, or product.

7. "FACTS" includes all evidence including documents concerning thereof, and witnesses knowledgeable of the same.

8. "PERSON" means any natural person, firm, association, organization, partnership, business, trust, corporation, or public entity.

9. "PTO" means the United States Patent and Trademark Office.

10. "FDA" means the United States Food and Drug Administration.

11. "NDA" means New Drug Application.

12. "ANDA" means Abbreviated New Drug Application.

13. "VENLAFAXINE" means the compound 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol commonly known as venlafaxine, as well as all compositions, formulations, and preparations containing venlafaxine, including without limitation VENLAFAXINE and other pharmaceutically acceptable salts of venlafaxine.

14. "EFFEXOR" means the VENLAFAXINE product sold by WYETH as Effexor®.

15. "EFFEXOR XR" means the VENLAFAXINE product sold by WYETH as Effexor® XR.

16. "PATENTS IN SUIT" means U.S. Patent No. 6,274,171 B1, U.S. Patent No. 6,403,120 B1, U.S. Patent No. 6,419,958 B2, and any other patent asserted by WYETH as infringed by IMPAX in the above-captioned action, individually or collectively.

17. "NAMED INVENTORS" means Deborah M. Sherman, John C. Clark, John U. Lamer, Steven A. White, and any other person listed as an inventor for the PATENTS IN SUIT, individually or collectively.

18. For the purposes of this notice only, "EXTENDED RELEASE FORMULATION" means a formulation which releases the active ingredient at a slower

rate than the immediate release formulation of the active ingredient such that the desired dosing frequency is or would be less than that for the immediate release formulation.

19. "WYETH'S REPLY" means the Plaintiff Wyeth's Reply to First Amended Counterclaims of Defendant Impax Laboratories, Inc. filed by WYETH in the above-captioned action on August 30, 2006, and any amendments thereto.

20. "ALZA" means Alza Corporation, and its past or present directors, officers, employees, agents, representatives or attorneys known to WYETH.

CERTIFICATE OF SERVICE

I hereby certify that on March 9, 2007, the foregoing document, DEFENDANT IMPAX LABORATORIES, INC.'S SECOND AMENDED NOTICE OF DEPOSITION OF WYETH PURSUANT TO FED. R. CIV. P. 30(b)(6), was served on counsel via U.S. Mail:

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Karen Jacobs Louden
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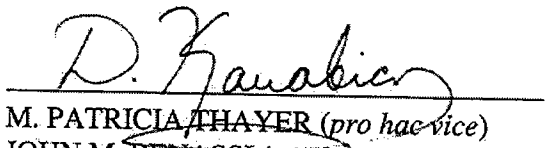
Dated: March 9, 2007



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SF 1354394 v4

PROOF OF SERVICE BY MAIL

I, Francesca Romero, declare as follows:

I am employed with the law firm of Heller Ehrman LLP, whose address is 4350 La Jolla Village Drive, 7th Floor, San Diego, California 92122. I am readily familiar with the business practices of this office for collection and processing of correspondence for mailing with the United States Postal Service; I am over the age of eighteen years and not a party to this action.

On March 9, 2007, I served the following:

DEFENDANT IMPAX LABORATORIES, INC.'S SECOND AMENDED NOTICE OF DEPOSITION OF WYETH PURSUANT TO FED. R. CIV. P. 30(B)(6)

on the below parties in this action by placing true copies thereof in sealed envelopes, addressed as shown, for collection and mailing pursuant to the ordinary business practice of this office, which is that correspondence for mailing is collected and deposited with the United States Postal Service on the same day in the ordinary course of business:

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I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this Proof of Service was executed on March 9, 2007 in San Diego, California.

Francesca Romero

Francesca Romero

SD 867019 v1

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH,)
)
Plaintiff,)
) C.A. No. 06-222-JJF
v.)
)
IMPAX LABORATORIES, INC.,)
)
Defendant.)

Friday, March 2, 2007
10:59 a.m.
Courtroom 4B

844 King Street
Wilmington, Delaware

BEFORE: THE HONORABLE JOSEPH J. FARNAN, JR.
United States District Court Judge

APPEARANCES:

MORRIS, NICHOLS, ARSHT & TUNNELL
BY: JACK B. BLUMENFELD, ESQ.
BY: KAREN JACOBS LOUDEN, ESQ.

-and-

FINNEGAN, HENDERSON, FARABOW
GARRETT & DUNNER, LLP
BY: BASIL LEWRIS, ESQ.
BY: LINDA WADLER, ESQ.

Counsel for Plaintiff

APPEARANCES CONTINUED:

MORRIS, JAMES, HITCHENS & WILLIAMS
BY: RICHARD HERRMANN, ESQ.

-and-

HELLER EHRMAN, LLP
BY: DANIEL KASSIBIAN, ESQ.

Counsel for Defendant

THE COURT: Next we're going to hear from Wyeth versus Impax, 06-222.

All right. You want to announce your appearances?

MS. LOUDEN: Yes, Your Honor. For plaintiff, Wyeth, Jack Blumenfeld and Karen Jacobs Louden from Morris Nichols. And presenting for Wyeth will be Bill Lewris of Finnegan Henderson and Linda Wadler.

MR. LEWRIS: Good morning, Your Honor.

THE COURT: Good morning. Welcome.

MR. HERRMANN: Good morning, Your Honor.

THE COURT: Good morning.

MR. HERRMANN: Richard Herrmann for defendant, Impax. And I have with me Daniel N. Kassibian from the Heller Ehrman firm.

THE COURT: All right. Thank you, Mr. Herrmann.

Welcome.

All right. With regard to defendant's motion to compel Interrogatory Number 35, which is Docket Item 76, I'm going to grant

the application, and I'm going to grant it in this context. You probably don't have it with you, but defendant's reply brief in support of motion to compel a response to Interrogatory Number 35.

If you go to Page 1, and at the end of the first paragraph of the introduction, Impax says this, The interrogatory simply asked Wyeth to identify the individual witnesses at Wyeth having information regarding the Alza formulation, and to state why -- the contentions as to why it was not obligated to notify the Patent & Trademark Office of the collaboration and prior art formulations.

That's, in my view, the thrust of the interrogatory, and the question that has to be answered. So I know you all have different views of the breadth of the interrogatory. That's as I'm going to characterize it in granting the motion.

And now you can talk if you want about the motion for entry of a protective order to strike and limit the scope of the Amended Notice of Deposition of Wyeth pursuant to 30(b)6.

MR. LEWRIS: Thank you, Your Honor. Your Honor, it's -- Impax's position, basically with respect to the Rule 30(b)6 notice is that Rule 26, they say, We're entitled to anything that's relevant.

Therefore, Wyeth put up a witness. We've given you 30 some odd topics, including one dealing with a reply to the counterclaims.

Basically, put up a witness who can address every conceivable question, every issue in this case. We've produced a million documents to them, over a million documents.

We've produced deposition testimony from the Teva case. We've produced to them expert reports from the Teva case.

They haven't taken a single deposition. So they say, We're not going to take these depositions. We're not going to look at your documents.

We're just going to give you every topic in the case. We want you to prepare a witness, in essence, to try your case in a deposition.

And we think that is entirely not

the function of Rule 30(b)6. They say that somehow we are attempting to hold back evidence. They have the documents. They know who the witnesses are.

Take a deposition. Don't tell us. Look at all of your documents, answer every conceivable question, feed all of that information to one or more expert witnesses and do it by 30(b)6. We don't think that's the appropriate way to go.

We tried to compromise with them. We provided, -- which is outlined in our opening brief at Pages 5 through 9 -- to put it mildly, a very generous collection of topics to put witnesses on, but that wasn't enough.

They say, Gee, this isn't enough. Because we looked at the depositions in the Teva case. We looked at a witness who gave it -- who couldn't answer a question.

Well, that's not surprising if a witness couldn't answer a question after ten years. They say we didn't refresh his recollection. They have a million documents to refresh any witness' recollection if that's what

they want to do.

But to not take any deposition in the case and to right out of the box basically say, Prepare your whole case and do it through a 30(b)6 witness or witnesses is entirely inappropriate. It's burdensome. And it's not the way discovery is conducted.

THE COURT: All right. Thank you.

MR. KASSIBIAN: Your Honor, I'd like to note that we just didn't hear, other than rhetoric, the applicable rule. Rule 26(b) sets forth with specificity the factors to be considered as to whether a particular discovery request is burdensome.

And in their briefing, none of it's addressed. We raise it in our briefing. But all they throw back is, It's too much. It's too much.

And that's all relevant to or relative to the issues in this case, the size of the parties. It's all the amount in controversy, the importance of the issues in stake in the litigation, and the importance of the proposed discovery in resolving these issues.

Now, Mr. Lewris also points to the fact that in his view, this notice, which is 34 topics, points to every issue in this case. I'm just perplexed by that statement, because we don't ask any questions about infringement. We don't say, What's your invalidity position?

Those are two high-level, big issues we don't really touch on. And yet he says every issue in this case.

To the contrary, if you look at each one of these requests, they are limited in scope, and they go to particular factual inquiries. Now, the one that Mr. Lewris does raise is their reply to counterclaims.

And in their leave briefing, they call this seeking contention discovery and overbroad. And I'll address that head on, because that particular pleading, if you thumb through it, it has denials to our answer, which set forth factual statements.

And then Wyeth went a step forward, and for whatever reason, pled affirmative facts in their reply to counterclaims. So they're just saying denied. Admit. Denied. Admit.

They set forth a bunch of facts. And so it's clear to us that in an operative proceeding, they set forth facts. And if they intend to prove those facts, the corporation must have knowledge as to those facts.

And, therefore, we're allowed to conduct a deposition as to those facts.

THE COURT: Assuming that your notice is not burdensome, and that you fully intend to cover the topics that you've noticed with a 30(b)6 witness, --

MR. KASSIBIAN: Yes, sir.

THE COURT: -- how long is that deposition going to take?

MR. KASSIBIAN: Well, Your Honor, we've tried to group the topics into -- I think there are probably five major categories. I would honestly be speculating, because let's say with prosecution there's --

THE COURT: Let's say when you prepare a notice for a deposition, that's something you probably should have thought about, how long it would take to examine the produced witness. Because -- and I don't want to go

through the litany, but that's the kind of factors that I might consider in coming to a finding of whether your notice is overly broad.

Again, you know, we decide these kinds of motions in a vacuum. So you kind of develop decisional dynamics.

So let me see: Is this a fair notice? And so if it's going to take eight days to do this deposition, it's probably not fair. That was one, you know, on the time factor.

If it's going to take seven hours as the rule provides, well, if you think you can get it done in seven hours, you know, you get one shot. And you think you're going to talk about all these topics, and you know that you're probably not going to be able to come back for a redeposition, then it might not be overly broad.

I just don't know. Let me ask you this question: Without the time factor, what on each topic, do you definitively expect to get? Do you expect to get material that will allow you to file Request for Admissions?

Do you expect to get material that will or testimony that will lead you to other

discoverable discovery opportunities? Or what is it you think you're going to get from all these topics?

MR. KASSIBIAN: I think in most cases, as to most topics we're looking for evidence that we would submit at trial.

THE COURT: So this is -- you expect to get substantive evidence out of this deposition on all those topics? And can you --

MR. KASSIBIAN: On most, I think.

THE COURT: If I asked you to do a chart, could you relate the topics to specific issues and the type of evidence you would anticipate, substantive evidence you would anticipate getting?

MR. KASSIBIAN: I have -- I didn't want to go through it topic by topic, but I do have two categories of topics. As I explained, Your Honor, not every topic -- I should note that one of our topics, for example, last topic is a standard one about document collection in this case.

I mean, that doesn't obviously go to evidence for trial. But other topics say

prosecution topics. This isn't something that we just asked in the vacuum.

We had very specific parts of the statements in the patent, and during prosecution that we have questions about. And so we've noticed those specific topics and said what kinds of questions we're going to ask about them.

The other major topic that's come up a lot in the briefing is the conception and reduction to practice. There's been a lot of briefing back and forth about that.

They call it a contention interrogatory. We say simply, No, you've given us some very preliminary facts, i.e. the date and the people involved in our Interrogatory Number 2. You don't explain why, what these people did. You refuse as irrelevant.

And so we're going to go to the next step and ask Wyeth what do they know about this? They obviously know something more than a date and who the people were. And they name a whole bunch of people.

THE COURT: It sounds like we could be into day four.

MR. KASSIBIAN: Well, Your Honor, it definitely isn't going to go to day seven. I doubt it will take seven hours, but they have produced, as they admit, produced a million documents here.

THE COURT: What time frame would you anticipate for the topics noticed?

MR. LEWRIS: Your Honor, this could go on for many, many days. What Mr. Kassibian effectively said, Your Honor, is what I said at the outset, what they want to do is collect all their evidence for trial through the first 30(b)6 and only deposition in the case.

THE COURT: That's what it sounds like.

MR. KASSIBIAN: Well, Your Honor, like I said, as I just mentioned a key issue and dispute in this case, there's no argument about that, is infringement. I don't think Mr. Lewris points to any topics that goes to that.

On invalidity, obviously, there are certain underlying facts to invalidity that are in this topic. But we don't ask what do you think about this prior art? What do you think

about that prior art? To the extent they were actually participants in a joint development, they might want that.

THE COURT: Here's the good news. I don't know how to litigate a patent case. I hope never to learn.

But what I would like, I'm going to grant the motion, but it's with no prejudice to any renoticing you might do. But I would suggest that any renoticing of the deposition be done with a thought toward the amount of time on each substantive topic.

And that way if there is a similar application to the present one, you'll come back in front of me with sort of a plan for the deposition, which will allow me to review it and then make a decision whether the noticing is overly broad or not.

So I'm going to grant the motion, and we'll certainly -- with no prejudice to renoticing the deposition. And then you are free to file whatever you want against the new notice.

MR. LEWRIS: Thank you, Your Honor.

MR. KASSIBIAN: You mentioned a

plan. I just wanted to get the parameters down.

You obviously mentioned time. Was there any specifics you wanted? I'm happy to provide --

THE COURT: There's a lot of patent lawyers here. Ask them what they do.

Did you want to address 306?

Somebody said three days.

MR. KASSIBIAN: If you want to give me three days, I'll take three days now.

THE COURT: I want you to litigate your own case. I just want to be like --

MR. KASSIBIAN: Well, Your Honor, we're trying to. We're trying to move forward, and unfortunately there's a slew of documents --

THE COURT: I think the notice has correctly been attacked as overly broad. It doesn't say anything about what issues you want to talk about or anything.

I think everything you've told me seems like fair discovery, but I think you have to have a plan of what you want to know. So you may need a little more -- well, I'm not going to get into it.

What do I know? I don't know how to litigate a patent. I'm just going to grant the motion and suggest to you that you develop a little more of a concrete plan.

So that when he attacks your notice, you'll be able to show me something that tells me whether, on the type of witness you've noticed, the topics you want to cover are fair and not overly burdensome. Somebody says three days, so I don't know.

MR. LEWRIS: That didn't come from us, Your Honor.

MR. KASSIBIAN: Well, with a million documents, I don't think that that would be --

THE COURT: Yeah. It could be ten days.

MR. KASSIBIAN: -- unburdensome. And again, given the context of the parties and the size of Wyeth and the issue --

THE COURT: It could be whatever, but right now based on the notice that I read and the premises of a motion filed, I'm going to grant it. And again, you have -- there's no prejudice to you to renotice and no comments

about what the topics you intend to notice on or anything else.

MR. KASSIBIAN: Your Honor, if I may address one other issue just in case it concerns the Court. One thing Wyeth has said consistently is you should go first with personal depositions and try to find people who know things.

I don't see any support for that without going forward with 30(b)6 that meets your criteria. I just want to make sure that's the case and that argument didn't hold with the Court, because I think that's what we might do, a personal deposition first. But we might come back here with what the Court asked for.

THE COURT: That's okay. I mean, I just don't know.

MR. KASSIBIAN: All right.

THE COURT: Somebody once said -- there was a lawyer in town who back in the day when they used to assign you to criminal cases and I was working in the Public Defender's Office, they assigned a real estate officer as a court-appointed attorney for a defendant. And the first thing he did was do a title search on

the prison.

That's about where I am now and how I would litigate a patent case. I have no clue. So I think you're a lot more knowledgeable than I am, and I'm going to credit that and leave you to your own devices.

MR. KASSIBIAN: All right. Thank you, Your Honor.

THE COURT: Thank you.

All right. Thank you.

(Hearing before Judge Farnan concluded at 11:27 a.m.)

State of Delaware)
)
New Castle County)

CERTIFICATE OF REPORTER

I, Heather M. Triozzi, Registered Professional Reporter, Certified Shorthand Reporter, and Notary Public, do hereby certify that the foregoing record, Pages 1 to 19 inclusive, is a true and accurate transcript of my stenographic notes taken on March 2, 2007, in the above-captioned matter.

IN WITNESS WHEREOF, I have hereunto set my hand and seal this 5th day of March, 2007, at Wilmington.

Heather M. Triozzi, RPR, CSR

EXHIBIT D

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March 13, 2007

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VIA EMAIL
CONFIRMATION COPY VIA U.S. MAIL

Wyeth v. Impax Laboratories, Inc., Civil Action No.: 06-222 (D. Del.)

Dear Daniel:

We are writing in response to your letter of March 9, 2007, regarding Impax's Second Amended Notice of Deposition of Wyeth Pursuant to Fed. R. Civ. P. 30(b)(6) ("Impax's Second Amended Notice"). At the outset, we disagree with your assertion, on page 1 of your March 9th letter, that you have "substantially narrowed the Notice." To the contrary, Impax's Second Amended Notice consists of 32 separate topics, whereas Impax's First Amended Notice contained 34 topics. Moreover, Impax's Second Amended Notice is substantially identical in topics and scope to your First Amended Notice, with a few minor exceptions. Indeed, in some cases, Impax has *expanded* the scope of topics that were previously noticed. As such, the Second Amended Notice is objectionable for at least the same reasons as Impax's First Amended Notice, which was the subject of Wyeth's Motion for a Protective Order, which the Court granted on March 2, 2007.

Your attempt to reorganize the topics into categories and assign time-frames to each of those categories does nothing to alleviate the oppressive, overly burdensome nature of Impax's Second Amended Notice. Irrespective of how long Impax expects to spend on each category of topics during the deposition, Wyeth would still be required to prepare one or more witnesses on topics that remain practically boundless in scope. As just one example, Topic 3, which is directed to "FACTS relating to the evolution of the composition and formulations of EFFEXOR XR and the development thereof from June 1990 through July 2002," covers on its face over 10 years of research and development, and, as per Impax, should be interpreted to "include" (but is not *limited* to) "modification to the formulations during that period, methods of manufacturing, when and where they were developed, who developed them, and what materials and methods were used to develop them." As we have previously noted with respect to the substantially similar noticed topic (*e.g.*, topic 3 of Impax's First Amended Notice), the topic encompasses, for example, pharmaceutical formulation; dissolution; stability; scale-up to commercial production; clinical trials on safety, bioavailability, and efficacy; clinical batch manufacturing, commercial manufacturing, and labeling. It also embraces testing and use of Effexor XR for the treatment of depression, the treatment of social

anxiety disorder, the treatment of generalized anxiety disorder, and the treatment of panic disorder, and further includes regulatory matters pertaining to Effexor® XR, encompassing 12 years of regulatory filings, correspondence, and label changes.[1] Yet this is just one of two topics that Impax alleges it will cover in only 4 hours of deposition testimony. Without further guidance as to what Impax is actually interested in, we are frankly at a loss as to how Wyeth can reasonably prepare a witness or witnesses to cover this one topic alone, let alone the full panoply of subject matters embraced by the remaining topics.

Furthermore, inserting the words "FACTS showing," "FACTS relating to," "FACTS evidencing," and the like, does not make Impax's manifestly unreasonable Rule 30(b)(6) notice acceptable, especially given both Impax's expansive definition of "FACTS" ("all evidence including documents . . . and witnesses knowledgeable of the same") and the sheer volume of "FACTS" that each such topic could potentially embrace. Nor does it alter the fact that a number of Impax's noticed topics still essentially seek Wyeth's contentions. *See Pharmacia & Upjohn Co. v. Sicor, Inc.*, C.A. No. 04-833 (KAJ) D. Del. Oct. 11, 2005 (Tr. at 36); *See also, ArthoCare Corp. Smith & Nephew, Inc.*, C.A. No. 01-504 (SLR)(D.Del. Oct. 15, 2002 (Tr. at 13-14)). As Wyeth pointed out in its Motion to Strike, this Court has emphasized that a 30(b)(6) deposition is an improper venue to seek a party's contentions. *See, e.g., Axiohm IPS, Inc. v. Epson Am., Inc.*, C.A. No. 00-420 (SLR) (D. Del. Mar. 28, 2001) (Tr. at 4.)("[W]e don't do contention depositions in this district. . . . "). Indeed a 30(b)(6) deposition is a particularly inappropriate vehicle for discovering a party's contentions in a patent case. *See McCormick-Morgan, Inc. v. Teledyne Indus., Inc.*, 134 F.R.D. 275, 287 (N.D. Cal. 1991); *rev'd on other grounds*, 765 F.Supp. 611 (N.D. Cal. 1991).

During the March 2, 2007 hearing on this issue, Judge Farnan agreed that Impax's First Amended Notice was correctly attacked as overbroad in that "[i]t doesn't say anything about what issues you want to talk about . . ." (Tr. at 15). We are therefore surprised and disappointed that, with the exception of the addition of several subject titles, Schedule A of Impax's Second Amended Notice presents essentially the same laundry list of information that Impax sought previously. This mere addition of organizing titles fails to ameliorate the overbreadth of Impax's notice, leaving Wyeth with the impossible task of having to guess as to the scope of the topics its witness should be prepared to testify on. *See Reed Bennet*, 193 F.R.D. 689, 692 (D. Kan. 2000) (granting in part motion to quash or modify 30(b)(6) notice because defendant could not identify the outer limits of the area of inquiry noticed). Thus we disagree with your assertion, on page 2 of your March 9th letter, that, for many of the topics, "the subject matter has been set forth with additional particularity."

---

[1] We recognize that Impax has eliminated "toxicology, quality control, animal testing, purchasing and qualification of raw materials, [and] packaging" from the scope of Topic 3. This does little, if anything, to minimize Wyeth's burden in responding to Topic 3, given the sheer breadth of the topic.

Furthermore, Wyeth objects to the organizing titles as incorrect, misleading, and as further broadening the scope of topics. For example, several organizing titles, such as titles I, IV, V, VII, and VIII amount to no more than incendiary, litigation-driven allegations of invalidity and inequitable conduct. And, by way of example, title VI, which reads "FACTS SUPPORTING STATEMENTS IN THE PATENTS OR REQUIRED TO UNDERSTAND THEM ..." broadens Topic Nos. 18-22, for example, to the extent it seeks information "required to understand" the various statements in the patents-in-suit cited in those topics.

With respect to additional particular failings of Impax's notice, the currently noticed topics are further objectionable for at least the reasons set forth below. Please be advised that this is not a comprehensive list of objections, but representative of the many problems Wyeth has with Impax's Second Amended Notice.

Impax's Topics Lack Reasonable Particularity and are Unreasonably Broad and Unduly Burdensome

Impax's Topic Nos. 1-11, 16-17, and 20-32 run afoul of the reasonable particularity requirement of Rule 30(b)(6), are unreasonably broad and burdensome, and embrace irrelevant subject matter in contravention of Rule 26. As just one example, Topic 16 seeks deposition testimony regarding "WYETH's knowledge and research prior to July 2002, demonstrating or refuting" that the claimed extended release formulations provided a therapeutic blood plasma concentration of venlafaxine over a 24-period with diminished incidences of nausea and emesis. This one topic encompasses virtually any document related to the *in vivo* testing of Effexor XR over almost a decade. This one broad topic alone covers years of research and development, involving untold numbers of people.

As another example, Topic 29 is directed to "strategies to shift or switch the subscription and/or the consumption of EFFEXOR XR to desvenlafaxine succinate, to be marketed as Pristiq or as another brand name in the United States" from December 2005 to the present. More particularly, given that Effexor XR contains the same active ingredient as Effexor, and that over a decade of actual marketplace data is available with which to compare the two products, Impax provides no explanation of the relevance of comparing Effexor XR to a prospective product, not even on the market and containing a different active ingredient. This topic is thus on its face irrelevant to any claim or defense, and would require Wyeth to needlessly prepare a witness to cover years of such "alleged strategies" by identified persons having no connection with the development of Effexor XR or the prosecution of the patents in suit. Similarly, topic 32 also embraces irrelevant subject matter, such as sales forecasts and profit margins.

Topic 31 serves as further illustration. This topic seeks testimony on "[a]ll correspondence with its advertising agencies involved in advertising EFFEXOR and EFFEXOR XR." This topic potentially embraces a host of communications involving issues having no relevance to any issue pending in this case, including invoices, communications regarding logistics of advertising efforts, contracts, proposals, confidentiality agreements, and a host of other completely irrelevant issues.

As was the case with Impax's First Amended Notice, the above listed topics cover a large amount of irrelevant information, and appear designed to impose an impossible burden on Wyeth to prepare a witness to cover these topics.

Impax's Second Amended Notice Seeks Contention Discovery, Which Is Not Appropriate for a Rule 30(b)(6) Deposition

Topic Nos. 1, 9, 12, 14, 16-17, 20-22, 25-26 in essence seek, either in whole or in part, Wyeth's contentions on various issues. As we have mentioned in the past, such contention topics are not appropriate for a Rule 30(b)(6) deposition in the District of Delaware.[2] And, as mentioned above, the fact that the topics ostensibly seek "FACTS" and do not explicitly recite the word "contention" does not alter this conclusion. Therefore, Impax is not entitled to Rule 30(b)(6) deposition testimony on the above-identified topics seeking contentions.

Impax's Second Amended Notice Improperly Seeks Attorney Client Privileged and Attorney Work Product Information

Impax's Topic Nos. 1-2, 12, 14, 20-25 impinge upon the attorney client privilege and/or attorney work product immunity. Couching the request in terms of "non-privileged information," "FACTS showing" or the like does not alter the fact that issues of privilege are inextricably intertwined with the requested discovery. Indeed, the attorney client privilege also extends to technical information communicated between attorney and client for the purpose of securing legal advice. *See SmithKline Beecham Corp. v. Apotex Corp.*, 232 F.R.D. 467, 480 (E.D. Pa. 2005); *see also Conner Peripherals, Inc. v. Western Digital Corp.*, 1993 WL 726815 at * 3 (N.D. Cal. June 8, 1993) (cited at page 3 of your December 15th letter). Because the requested discovery is so intertwined with issues of attorney client privilege and/or work product immunity, it is best conducted through means other than a Rule 30(b)(6) deposition.

Impax's Second Amended Notice Improperly Embraces Expert Opinion

Topic Nos. 18-22, 26-28, and 30 embrace expert opinion. Such discovery is appropriately conducted through contention interrogatories, which can be supplemented, if necessary, due to developments that occur during expert discovery.

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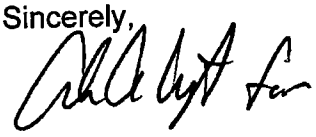
[2] *Axiohm IPS, Inc. v. Epson Am., Inc.*, C.A. No. 00-420-SLR (D. Del. Mar. 28, 2001) (transcript of hearing before Chief Judge Robinson at 4) ("[W]e don't do contention depositions in this district."); *Tiegel Manu Co. v. Globe Union, Inc.*, C.A. No. 84-483 at 14 (D. Del. Oct. 5, 1984) (noting that "[i]t has been the consistent position of this Court" that witnesses should not be required to testify as to contentions; instead, contention discovery is confined to interrogatories).

Impax's Second Amended Notice Is Unacceptable

In short, we are dismayed at Impax's approach of simply repackaging the same objectionable topics with only slight, and virtually meaningless, modifications. Wyeth is still unable to prepare a witness or witnesses because Impax has failed to define appropriate topics with the required particularity. Moreover, Impax's Second Amended Notice is unacceptably burdensome, as we have continually noted.

We are, as always, willing to discuss ways in which the topics in Impax's Second Amended Notice, could be narrowed or eliminated. We understand, however, that you intend to file a motion to compel. Please inform us immediately if Impax opts not to file such a motion.

Sincerely,



Barbara R. Rudolph

cc: Mary B. Matterer, Esq. (via e-mail)

EXHIBIT E

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT F

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT G

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

WYETH, **Plaintiff,** **v.** **TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.,** **Defendants.**	03-CV-1293 (WJM) **MARKMAN OPINION**

This matter comes before the Court on the parties' submissions seeking construction of four disputed claim terms found in the patents-in-suit. Having taken into consideration the parties' submissions and their arguments made during the *Markman* hearing, the Court construes the disputed claim terms as follows.

BACKGROUND

This is an Abbreviated New Drug Application ("ANDA") patent infringement action. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. ("Teva") filed an ANDA seeking to market a generic version of Wyeth's Effexor® XR. Wyeth filed suit, alleging Teva's generic extended release venlafaxine formulation infringes three of its patents: U.S. Patent Nos. 6,274,171 B1 (the "'171 patent"), 6,419,958 B2 (the "'958 patent"), and 6,403,120 B1 (the "'120 patent"). The three patents are related and share an essentially identical specification.

Wyeth charges Teva with infringement of claims 20-25 of the '171 patent, claims 1-6 of the '958 patent, and claims 1, 2, 13 and 14 of the '120 patent. These claims are all method claims and are directed towards a method of administering an extended release formulation of venlafaxine hydrochloride that provides a therapeutic blood plasma concentration of venlafaxine over twenty-four hours. The specification states that the extended release formulation provides two advantages over the immediate release formulation. First, it eliminates the sharp peaks and troughs in blood plasma drug levels caused by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. '171 patent, col. 2, lines 24-28.[1] Thus, rather than take two to three doses a day, patients need only take the extended release formulation once a day. Second, it reduces the side effects experienced by patients who have taken the immediate release tablets. *See id.* at col. 2, lines 46-55. The extended release formulation was found to reduce the incidence of nausea and emesis (the act of vomiting). According to Wyeth, these two advantages provided improved patient compliance and tolerability, making Effexor® XR a blockbuster drug. (*See* Wyeth's Br. at 2).

Although the named inventors attempted to develop an extended release formulation in the form of a tablet, they failed, finding it "impossible" to achieve a sustained release tablet formulation. Col. 10, lines 53-57. They did, however, succeed in developing a film-coated spheroid formulation that could be administered in a capsule. The specific formulation they found worked was composed of "venlafaxine hydrochloride, microcrystalline cellulose and,

[1]Because the patents-in-suit share an essentially identical specification, all future citations will be to the '171 patent unless otherwise noted.

optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose." Col. 2, line 67 - col. 3, line 2.

Prior to submitting their *Markman* briefs, the Court required the parties to submit a Joint Claim Construction Chart ("Chart") setting forth the claim terms in dispute and the parties' respective proposed constructions for each term. The parties identified four disputed claim terms: "extended release formulations," "spheroid," "with diminished incidence(s) of nausea and emesis," and "encapsulated." (*See* Chart). For claim construction purposes, the following claims are illustrative of how these terms are used. Claims 20 and 21 of the '171 patent recite:

> 20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.
>
> 21. A method for eliminating the troughs and peaks of drug concentration in a patients [sic] blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Claims 1 and 14 of the '120 patent recite:

> 1. A method for providing therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150 ng/ml, said formulation containing venlafaxine hydrochloride as the active ingredient.
>
> 13. The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid.

DISCUSSION

I. Law of Claim Construction

The Federal Circuit en banc recently reaffirmed the claim construction methodology articulated by *Markman v. Westview Instruments, Inc.*[2] and its progeny and clarified the role that dictionaries play in claim construction. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). In *Phillips*, the Federal Circuit reestablished the primacy of the intrinsic evidence – the claims, specification and prosecution history – and reclassified dictionaries as part of the less significant extrinsic evidence. In doing so, the Federal Circuit emphasized the need to construe the claims in their proper context, which is the specification. *Id.* at 1321.

The objective of claim construction is to determine how a person of ordinary skill in the art would understand the claim terms. *Id.* at 1313, 1324. Generally, claim terms are given their ordinary and customary meaning. *Id.* at 1312-13 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). That meaning "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1313. In determining the ordinary meaning of claim terms, the person of ordinary skill in the art is deemed to read the claim terms in the context of the entire patent, including the particular claims in which they appear and the specification. *Id.* at 1313.

The claims "provide substantial guidance as to the meaning of particular claim terms." *Id.* at 1314. Oftentimes, the context in which a term is used in asserted and unasserted claims

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[2]52 F.3d 967 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

"can be highly instructive." *Id.* Further, differences among claims can provide useful insight into a term's meaning. *Id.*

But the claims cannot be looked at in isolation; rather, they must be considered in view of the specification. *Id.* at 1315. The specification is considered to be the "single best guide" for construing the claims. *Id.* The specification may reveal whether the patentee acted as his own lexicographer by giving a claim term a special definition. *Id.* Or, it may show that the patentee intentionally disclaimed claim scope. *Id.* In either case, the patentee's intent is dispositive. *Id.*

A court should also consider the prosecution history, if it is in evidence. *Id.* at 1317. The prosecution history "consists of the complete record of the proceedings before the [Patent and Trademark Office ("PTO")] and includes the prior art cited during the examination of the patent." *Id.* (citing *Autogiro Co. of Am. v. United States*, 181 Ct. Cl. 55, 384 F.2d 391, 399 (1967)). Although it "often lacks the clarity of the specification and thus is less useful for claim construction purposes," the prosecution history sheds light on the PTO's and inventor's understanding of the patent. *Id.*

A court may, in its discretion, consult extrinsic evidence, i.e., dictionaries, treatises, and expert and inventor testimony, when construing claim terms. *Id.* A court may consult extrinsic evidence to educate itself about the field of the invention and to aid its understanding of what one of ordinary skill in the art would understand a claim term to mean. *Id.* at 1319. But extrinsic evidence is "less significant" and "less reliable" than intrinsic evidence because it gives meaning to a claim term in the abstract, rather than in the particular context of the patent. *Id.* at 1317-18. Thus, although it may play a supporting role in claim construction, extrinsic evidence may not be used to contradict an unambiguous meaning established by the intrinsic record. *See id.* at 1324.

II. The Disputed Claim Terms

1. "extended release formulation"

Wyeth contends that "extended release formulation" should be given its ordinary meaning and construed as "[a] formulation which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the dosing frequency is once-a-day rather than the plural daily dosing for the immediate release formulation." (Chart). Teva asserts that the patentees acted as their own lexicographers by identifying certain ingredients that must be present in the formulation. Teva asserts that "extended release formulation" means "[a] formulation comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration." (*Id.*, emphasis added). Because the Court agrees with Teva that the patentees acted as their own lexicographers, the Court will adopt Teva's proposed claim construction.

The Court begins by looking at the context in which the term "extended release formulation" is used in the claims of the patents-in-suit. Wyeth argues that the asserted claims demonstrate that the patentees did not intend to limit "extended release formulation" to any specific set of ingredients. Every asserted claim recites: "A method . . . which comprises administering orally to a patient in need thereof, an . . . extended release formulation . . ., said formulation containing venlafaxine hydrochloride as the active ingredient." (*See, e.g.*, '171 patent, claim 20, emphasis added). Wyeth argues that if in fact "extended release formulation"

encompassed particular ingredients, including venlafaxine hydrochloride, then the limitation "said formulation containing venlafaxine hydrochloride as the active ingredient" would be superfluous. (Wyeth's Br. at 11). According to Wyeth, if "extended release formulation" already included venlafaxine hydrochloride, then there is no need for the claims to specify the active ingredient. Thus, argues Wyeth, "extended release formulation" does not include any particular ingredients.

Wyeth also contends that the doctrine of claim differentiation supports its broad construction of "extended release formulation." The doctrine of claim differentiation gives rise to a presumption that a limitation added in a dependent claim is not present in the independent claim. *Phillips*, 415 F.3d at 1314-15. Comparing independent claim 1 of the '120 patent with dependent claim 3, Wyeth argues that the doctrine creates a presumption that "extended release formulation" does not include specific ingredients. (Wyeth's Br. at 13). Independent claim 1 recites: "A method . . . which comprises administering orally to a patient in need thereof, an extended release formulation . . ., said formulation containing venlafaxine hydrochloride as the active ingredient." '120 patent, claim 1 (emphasis added). Dependent claim 3 recites: "The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose." '120 patent, claim 3 (emphasis added). Because claim 3 includes the additional limitation of specific ingredients, the Court agrees with Wyeth that a presumption arises that claim 1 does not include that limitation. Thus, the Court agrees with Wyeth that the plain language of the claims implies that "extended release formulation" does not include specific ingredients.

Teva does not dispute that the claims, on their face, imply a broad construction for "extended release formulation." Rather, Teva argues that the presumption the broader construction applies is overcome by the narrow definition given to "extended release formulation" by the patentees in the specification. This Court agrees.

The patentees defined "extended release formulation" several times in the specification. In the abstract, they disclosed:

> More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlfaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

'171 patent, Abstract. They reiterated this same restrictive definition in the "Brief Description of the Invention:"

> The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

'171 patent, col. 2, line 62 - col. 3, line 2. Only after setting forth this description of their invention, did the inventors then go on to address the preferred embodiments of their invention. *See* '171 patent, col. 3, lines 5-62. Similarly, in the "Detailed Description of the Invention," the patentees defined "extended release formulations" by their ingredients:

> The extended release formulations of this invention are comprised of [venlafaxine] hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or

> spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose [sic] to provide the desired level of coating . . . .

'171 patent, col. 4, lines 9-15 (emphasis added).

Wyeth asserts that these statements merely identify a preferred embodiment of the invention. The Court disagrees. Because the specification definitively states that the "extended release formulations" of the invention are limited to particular ingredients, the Court finds that the patentees acted as their own lexicographers and limited the meaning of "extended release formulation." *See Astrazeneca AB v. Mutual Pharm. Co.*, 384 F.3d 1333, 1339-40 (Fed. Cir. 2004) (finding that the inventors acted as their own lexicographers and limited the term "solubilizer" to surfactants by stating in the specification that "[t]he solubilizers suitable according to the invention are defined below", and later describing the suitable solubilizers as surfactants).

Moreover, the specification provides additional support for a narrow construction of "extended release formulation." Although it is improper to limit the claims based on the preferred embodiments, the Federal Circuit has stated that the "preferred embodiments can shed light on the intended scope of the claims." *Id.* at 1340. Here, the specification sets forth seven examples describing different embodiments the named inventors worked with. Each and every embodiment of an "extended release formulation" recited in these examples includes venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC[3] coated with ethyl cellulose and HPMC. *See, e.g.*, '171 patent, col. 5, line 33 - col. 10, line 57. The fact that all of these examples use the same core set of ingredients buttresses the conclusion that "extended release

[3]"HPMC" is the abbreviation for "hydroxypropylmethylcellulose."

formulation" should be narrowly construed. *See Astrazeneca*, 384 F.3d at 1340-41 (finding additional support for a limited construction of "solubilizer" in the fact that "all of the solubilizers listed in the specification and used in the working examples were surfactants").

Further, the specification distinguishes the "extended release formulations" of the invention from extended release hydrogel tablet formulations. Wyeth admits that under its proposed construction, an extended release hydrogel tablet having the claimed *in vivo* characteristics may fall within the asserted claims. (*See* Wyeth's Br. at 16 n.6). The specification, however, discloses that the inventors' attempts to develop extended release hydrogel tablets were "fruitless" and teaches one of ordinary skill that it is "impossible to achieve" the desired dissolution rates using hydrogel tablet technology. Col. 4, lines 60-64; col. 10, lines 53-57. These statements were made without qualification. Accordingly, the specification supports construing "extended release formulation" more narrowly than Wyeth proposes. *See Cultor Corp. v. A.E. Staley Mfg. Co.*, 224 F.3d 1328, 1331 (Fed. Cir. 2000) ("Claims are not correctly construed to cover what was expressly disclaimed.").

Wyeth responds that the specification supports its broader, ordinary meaning of the term. Wyeth asserts that Teva ignores several portions of the specification which allegedly refer only to the "extended release formulation" as including venlafaxine hydrochloride. *See, e.g.*, '171 patent, Abstract ("This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant . . . .") (emphasis added); *Id.* at col. 2, lines 14-16 ("In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s [sic] component . . . .") (emphasis added); *Id.* at col. 2, lines 37-44 ("Hence, in

accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys . . . which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.") (emphasis added). Wyeth further asserts that its broad construction is supported by those portions of the specification that compare "extended release formulations" with immediate release formulations. *See, e.g.*, '171 patent, col. 2, lines 24-37 (contrasting blood plasma profiles for both types of formulations without reference to specific ingredients). And Wyeth contends that Table 1 in the specification supports a broader construction because it allegedly teaches an ordinary artisan how to screen for other useful inactive ingredients that may work in combination with venlafaxine hydrochloride to develop an extended release venlafaxine formulation. But there is no merit to Wyeth's arguments because they ignore those portions of the specification set forth above that explicitly characterize and limit the invention to a formulation containing specific ingredients.

When the term "extended release formulation" is looked at in its proper context in the specification, this Court believes that one of ordinary skill in the art would construe the term to include specific ingredients. The unequivocal language the patentees used when describing their invention – "the invention comprises an extended release formulation of", "[t]he formulations of this invention comprise" and "[t]he extended formulations of this invention are" – rebuts the presumption established by the doctrine of claim differentiation. *See, e.g.*, *Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1368-69 (Fed. Cir. 2000) (finding the presumption of claim differentiation overcome because the specification and prosecution history described the "protecting back panel" as one that must be relatively stiff). Although this may make certain

dependent claims coterminous and certain claim limitations superfluous, that result is inevitable and inescapable in a case such as this where the patentees act as their own lexicographers. *See Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1480 (Fed. Cir. 1998) ("[T]he doctrine of claim differentiation can not broaden claims beyond their correct scope, determined in light of the specification and the prosecution history and any relevant extrinsic evidence."); *Sule v. Kloehn Co., Ltd.*, 149 F. Supp. 2d 115, 128 (D.N.J. 2001) ("Claim differentiation is a guide, not a rigid rule. If a claim will bear only one interpretation, similarity will have to be tolerated.") (quoting *Autogiro*, 384 F.2d at 404) .

The portions of the prosecution history in evidence do not alter this conclusion. Although Wyeth contends that the prosecution history supports a broader construction because the method claims were allowed without limitation to specific ingredients, given the clear and unambiguous language in the specification, the Court believes that the prosecution adds, at most, nothing more than the claims themselves reveal. That being the case, the definition provided by the specification, which is the "single best guide to the meaning of a disputed term," shall be adopted. *Vitronics*, 90 F.3d at 1582.

Because the meaning of the term can be ascertained from the intrinsic record, the Court will not rely on extrinsic evidence that suggests a broader construction. *See Phillips*, 415 F.3d at 1324 (prohibiting the use of extrinsic evidence to contradict the unambiguous meaning provided to a claim term by the intrinsic evidence). That evidence takes the term out of its all-important context in the specification and, thus, will be given no weight.

In sum, "extended release formulation" means "a formulation comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC coated with a mixture of ethyl

cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration."

2. "spheroid"

Wyeth contends that "spheroid" means "[o]ne or more particles that are generally shaped like a sphere, although they do not have to be perfectly round", including "granules, beads and pellets." (Chart). Teva asserts that "spheroid" means "[o]ne or more particles that are generally shaped like a sphere and result from an extrusion and spheronization process." (*Id.*, emphasis added). Essentially, although the parties agree that "spheroid" means "one or more particles that are generally shaped like a sphere," they dispute whether the term should be limited to a particular manufacturing process. Because the intrinsic evidence does not narrow the meaning of "spheroids," which connotes shape, the Court will not limit its construction to a specific manufacturing process.

The term "spheroid" is contained in asserted claims 13 and 14 of the '120 patent. Wyeth argues that these claims are drawn broadly to include any "spheroid," regardless of the method of manufacture. Claim 13 recites: "The method of claim 1 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid." '120 patent, claim 13 (emphasis added). Claim 14 is similarly broad: "The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid." '120 patent, claim 14 (emphasis added). Thus, the plain language of the claims does not suggest that the term "spheroid" has anything other than its ordinary meaning. Morever, the specification

uses the ordinary meaning of "spheroid," equating "beads" with "spheroids" without any apparent limitation on the method of manufacture. *See* '171 patent, col. 4, lines 12-13 ("Formed as beads or spheroids, the drug containing formulation is coated . . . ."). This ordinary, unrestricted meaning is consistent with how "spheroid" is defined in a dictionary – "[a] body that is shaped like a sphere but is not perfectly round, esp. an ellipsoid that is generated by revolving an ellipse around one of its axes." Am. Heritage College Dict. 1310 (3d ed. 1993).

Teva does not dispute that Wyeth's construction comports with the ordinary meaning of the word "spheroid." (*See* Teva's Opp'n Br. at 23). Rather, it contends that in this case the patents do not support the broader definition because they only identify one method of manufacture – the extrusion and spheronization process. For example, in the "Background of the Invention," the patentees described the process they used for making "spheroids:"

> In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution.

'171 patent, col. 1, lines 38-47 (emphasis added); *see also* col. 5, lines 1-13 (stating that the addition of microcrystalline cellulose and HPMC made manufacture of spheroids with extruders possible); col. 6, lines 6-11 (stating that different extruders allowed spheroids to be made without HPMC).

Teva overreaches. Although the patents disclose only one method of manufacturing "spheroids" – the extrusion and spheronization process – it appears to be described as a preferred

method of manufacture, not the only method of manufacture. *See* '171 patent, col. 1, lines 38-47 (stating that the extended release formulations "may be formulated by" extrusion and spheronization, not must be formulated by this method). Teva appears to be attempting to import the preferred process into the claims. But there is no clear disclaimer of the term's ordinary meaning, nor do the patentees define "spheroid" as being limited to that method of manufacture. Further, the Federal Circuit has held that merely disclosing only one method of manufacture in the specification does not, by itself, limit the term to that one method. *See Vanguard Products Corp. v. Parker Hannifan Corp.*, 234 F.3d 1370, 1371-72 (Fed. Cir. 2000) (construing the word "integral" to define the relationship between layers in a gasket, and refusing to limit the formation of those layers by co-extrusion, the only manufacturing process disclosed in the specification and extolled in the prosecution history); *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 375 F.3d 1367, 1373 (Fed. Cir. 2004).

Teva raises one additional argument to support its narrow construction. It alleges that because the patentees neither described nor enabled the making of "spheroids" by any method other than by extrusion and spheronization, the term "spheroid" should be limited to maintain the validity of claims 13 and 14. (Teva's Br. at 28). Teva notes that the named inventors were aware of other methods of making "spheroids," but did not disclose them to the public. Absent that disclosure, Teva contends that the claims are not enabled or described. This argument is flawed. A court should not construe a claim term to preserve a claim's validity unless, "after applying all the available tools of claim construction," the claim term remains ambiguous. *Liebel-Flarsheim*, 358 F.3d at 911. Here, the term "spheroid" is not ambiguous and, therefore, the Court will not embark on a validity analysis at this time.

In conclusion, the Court finds that "spheroids" should not be limited to a particular method of manufacture. As such, the Court finds that "spheroids" means "one or more particles that are generally shaped like a sphere, although they do not have to be perfectly round."

3. "with diminished incidence(s) of nausea and emesis"

The parties agree that the meaning of the term "incidence" should include "frequency" of an occurrence or event. (Chart). They disagree, however, whether it should include "degree" or "level." (*See id.*).

The claims that contain this limitation are unilluminating. *See, e.g.*, '171 patent, claims 20, 22-23. Therefore, the Court begins by looking at the specification. Both parties refer to the same passage in the specification to support their construction:

> The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clincial trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

'171 patent, col. 2, lines 45-62 (emphasis added).

Both parties agree that the reference to "level," as used in the above passage, connotes degree. They disagree, however, on what affect, if any, that has on the meaning of "incidence."

Teva contends that the passage above distinguishes between "level," i.e., degree, and "incidence," i.e., frequency. Teva further points out that the claims do not use level or degree; rather, they only refer to "incidence." Wyeth contends that the passage equates "incidence" with "level," thereby broadening the meaning of the term to include degree. Wyeth also juxtaposes the above passage with an excerpt that appears earlier in the specification:

> With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

'171 patent, col. 2, lines 7-11 (emphasis added). Wyeth asserts that this passage demonstrates that when the patentees meant to refer to the number of patients experiencing a side effect, they did so by stating that they were "experienced by" or "occurs in" a certain "percent" of patients. Significantly, according to Wyeth, the patentees did not equate percent with "incidence." Thus, Wyeth asserts "incidence" is broader than frequency.

Wyeth's argument is inapt. Simply because the patentees did not use the word "incidence" in the earlier passage does not by itself redefine "incidence." Rather, that passage makes clear that the patentees were concerned with the number of patients experiencing side effects, not necessarily the severity of those side effects. Moreover, the abstract states that the invention "provides a lower incidence of nausea and vomiting than the conventional tablets." '171 patent, Abstract (emphasis added). Because the only discussion of the conventional tablets in the specification that is relevant to the term "incidence" concerns the percent of patients that experienced side effects, the abstract supports a narrow construction.

Ultimately, Teva appears to be correct that the patentees drew a distinction between "level" and "incidence." Although the specification refers to both terms, the claims only recite "incidence." If indeed "incidence" meant the same thing as "level," or was broader, it begs the question why the word "level" was used in the first place. The reason must be because the patentees meant to differentiate between the two terms. It is clear from the specification that when the patentees wanted to refer to "incidence," they did. Thus, the term "incidence" will be limited to its ordinary meaning as informed by the specification.

Lastly, it is worth noting that "[t]he fact that a patent asserts that an invention achieves several objectives does not require that each of the claims be construed as limited to structures that are capable of achieving all of the objectives." *Liebel-Flarsheim*, 358 F.3d at 908. Thus, the fact that the patents may discuss a reduced "level" and "incidence" of nausea does not require that claims using the word "incidence" encompass both benefits. In addition, the "incidence" limitation is not present in all of the asserted claims. *See, e.g.*, '171 patent, claims 21, 24-25; '958 patent, claims 2, 5-6. Therefore, to the extent that Wyeth suggests that a narrow construction of this term unjustifiably excludes one of the primary benefits of the invention, namely the reduction in degree of side effects, that is not the case for all asserted claims. The asserted claims that do not contain the "incidence" limitation are obviously broader and would read on such benefits.

Furthermore, to the extent that Wyeth relies on extrinsic evidence to support its broad construction, the Court does not find that evidence particularly helpful. The specification draws a clear distinction between "incidence" and "level." General dictionary definitions that allegedly support a broader construction ignore the context within which the patents use the term. *See,*

e.g., Concise Oxford Dict. of Current English 614 (5th ed. 1964) (defining "incidence" as "range, scope, extent, of influence"). The Federal Circuit in *Phillips* warned of relying on such definitions: "[H]eavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification." *Phillips*, 415 F.3d at 1321. In any event, other dictionaries define the term as limited to frequency. *See* Webster's Third New Int'l Dict. (Unabridged) 1142 (2002) (defining "incidence" as "rate, range, or amount of occurrence or influence . . . *sometimes*: the rate of occurrence of new cases of a particular disease in a population being studied") (emphasis in original); Taber's Cyclopedic Med. Dict. 1077 (19th ed. 2001) (defining "incidence" as "the frequency of new cases of a disease or condition in a specific population or group"). These dictionaries provide a common meaning that is more fitting given the distinction the specification draws between "incidence" and "level."

Wyeth's experts' opinions, which remove the term "incidence" from its proper context, are also given no weight. *See Phillips*, 415 at 1318 (stating that a court "should discount any expert testimony 'that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent'") (quoting *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998)). Further, these experts' opinions are countered by Teva's experts, who opine that the common meaning of "incidence" is consistent with only frequency. *See* Schoenfeld Expert Report ¶ 9; Morrow Expert Report ¶ 11.

Accordingly, the Court finds that "with diminished incidence(s) of nausea and emesis" means "a decrease in the number of patients suffering from nausea and vomiting compared to

patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day."

4. "encapsulated"

Wyeth asserts that "encapsulated" means "[a] formulation that is present in a capsule, i.e., one that is filled into a pharmaceutically acceptable capsule." (Chart). Teva essentially proposes two different constructions depending on how the Court construes the term "extended release formulation." If the Court construes "extended release formulation" broadly to not include any particular ingredients, Teva contends that "encapsulated" means "[a] formulation that is present in a capsule." (*Id.*). On the other hand, if the Court construes "extended release formulation" to include particular ingredients, Teva agrees with Wyeth's narrower construction. (*See, e.g.*, Teva's Br. at 29 ("If the Court adopts Teva's construction of the term 'extended release formulation,' there is no dispute concerning the term "encapsulated.")).

Although the Court disagrees with Teva's argument that the construction of the term "encapsulated" is contingent on the construction of "extended release formulation," there appears to be no need for this Court to perform an exhaustive analysis of how this term should be construed because the Court has adopted the narrower construction of "extended release formulation." That being the case, the parties do not dispute the meaning of the term "encapsulated." Accordingly, the Court finds that "encapsulated" means "a formulation that is filled into a pharmaceutically acceptable capsule."

CONCLUSION

For the aforementioned reasons, the Court construes the disputed claim terms as follows:

1. "extended release formulation" means "a formulation comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration;"

2. "spheroids" means "one or more particles that are generally shaped like a sphere, although they do not have to be perfectly round;"

3. "with diminished incidence(s) of nausea and emesis" means "a decrease in the number of patients suffering from nausea and vomiting compared to patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day;"

4. "encapsulated" means "a formulation that is filled into a pharmaceutically acceptable capsule."

Dated: September 6, 2005

s/ William J. Martini
William J. Martini, U.S.D.J.

EXHIBIT H

United States Patent [19]

McAinsh et al.

[11] **4,138,475**

[45] **Feb. 6, 1979**

[54] **SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION**

[75] Inventors: **James McAinsh; Raymond C. Rowe,** both of Macclesfield, England

[73] Assignee: **Imperial Chemical Industries Limited,** London, England

[21] Appl. No.: **833,339**

[22] Filed: **Sep. 14, 1977**

[30] **Foreign Application Priority Data**

Jun. 1, 1977 [GB] United Kingdom 23114/77

[51] **Int. Cl.**[2] **A61K 9/52;** A61K 9/54; A61K 9/58

[52] **U.S. Cl.** **424/19;** 424/20; 424/21

[58] **Field of Search** 424/19–22, 424/35, 362

[56] **References Cited**

U.S. PATENT DOCUMENTS

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OTHER PUBLICATIONS

Windholz et al., Merck Index 9th Ed. 1976, Merck & Co., Rahway, N. J. #7628, p. 1016, entry "Proprano-lol".

Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

Sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the spheroids comprising propranolol, or a pharmaceutically-acceptable salt thereof, in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose and/or a plasticizer.

9 Claims, No Drawings

SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION

This invention relates to a sustained release pharmaceutical composition and more particularly it relates to a sustained release pharmaceutical composition containing propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

Propranolol hydrochloride is an important medicament which is widely used throughout the world. It is a β-adrenergic blocking agent which is mainly used for the treatment of angina pectoris, cardiac arrhythmias and hypertension. The chemical name for propranolol is dl-1-isopropylamino-3-(1-naphthoxy)-2-propanol. This compound and its acid-addition salts, and processes of manufacture thereof, are claimed in our United Kingdom patent No. 994,918. Furthermore, pharmaceutical compositions comprising at least one of these substances in admixture with a pharmaceutically-acceptable diluent or carrier are claimed in our United Kingdom patent No. 995,800. The present invention relates to a new sustained release pharmaceutical composition which is not disclosed in, nor rendered obvious by, said patent No. 995,800 nor elsewhere in the art.

According to the invention there is provided a sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol or a pharmaceutically-acceptable acid-addition salt thereof in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose.

The term "spheroid" is well known in the pharmaceutical art, and means a spherical granule having a diameter of approximately 0.5 to 2mm. As a particularly suitable salt of propranolol there may be mentioned, for example, the hydrochloride. A suitable microcrystalline cellulose is, for example, the material sold as Avicel-PH-101 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa, U.S.A.). According to one embodiment of the invention the uncoated spheroids may, for example, contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of microcrystalline cellulose, respectively.

A suitable form of ethylcellulose is that having a viscosity in the range of 5 to 100 cps at 20° C. (U.S. National Formulary XIII) (content of ethoxy groups 44 to 51% by weight), and more particularly a viscosity of 50 cps at 20° C. (content of ethoxy groups 48 to 49% by weight). A suitable form of hydroxypropyl methylcellulose is that having a viscosity in the range 3 to 100 cps at 20° C. (U.S. National Formulary XIII), and more particularly a viscosity of 6 cps at 20° C. The film coat may, for example, comprise 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose, and more particularly 90% by weight of ethylcellulose and 10% by weight of hydroxypropyl methylcellulose. In addition, the film coat may optionally contain up to 20% by weight of a plasticizer, for example a vegetable oil, for example castor oil, or glycerol, or a glyceryl ester of a fatty acid, for example glyceryl triacetate or glyceryl monoricinoleate. The film coat may comprise 5 to 15% by weight of the coated spheroids, and preferably 9 to 10% by weight thereof.

The sustained release composition of this invention may, for example, contain 100 to 200mg., and more particularly 160mg., of the medicament, for example propranolol hydrochloride.

The sustained release compositions of this invention may be manufactured by well known pharmaceutical manufacturing methods. For example, the spheroids may be manufactured on a conventional spheroniser in which a horizontal, rough-surfaced plate rotates inside a stationary vertical cylinder, and then film coated in conventional manner in a perforated coating drum, and finally the film coated spheroids filled into hard gelatine capsules using a conventional encapsulation machine.

The invention is illustrated but not limited by the following Example.

EXAMPLE

Propranolol hydrochloride (60kg.) and microcrystalline cellulose (Avicel-PH-101; 40kg.) were blended together in a 450 litre planetary mixer. Water (50kg.) was added, and the mixer was run for 10 minutes until a homogeneous, plastic mass was obtained. The mass was extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1mm. diameter.

The damp extrudates (in batches of 15 to 20kg.) were placed in a spheroniser in which the rotating disc (diameter 68cm.) rotated at 300 to 400 r.p.m. The rotation was continued for 10 minutes, and the resulting spheroids were then dried at 60° C. in a fluidised bed drier. The dried spheroids were passed over a 1.4mm. screen, and those which passed through were subjected to a 0.7mm. screen. The over-and under-sized spheroids were discarded.

Acceptable spheroids (100kg.) were placed in a perforated coating drum fitted with a 0.5mm. screen and rotating at 17 r.p.m. A film formulation consisting of ethylcellulose (9kg.) and hydroxypropyl methylcellulose (1kg.) dissolved in a mixture of dichloromethane (100 liter) and methanol (100 liter) was sprayed onto the rotating spheroids at a rate of 750ml. per minute using a standard airless spray system. The resulting film coated spheroids were passed over a 1.4mm. screen to remove any aggregates, and then filled into hard gelatine capsules using a conventional encapsulation machine, such that each capsule contained 160mg. of propranolol hydrochloride. There was thus obtained a sustained release composition containing propranolol hydrochloride.

What we claim is:

1. A sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol, or a pharmaceutically-acceptable acid-addition salt thereof, in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose or ethycellulose and hydroxypropyl methylcellulose.

2. The composition claimed in claim 1 in which the uncoated spheroids contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of non-water-swellable microcrystalline cellulose, respectively.

3. The composition claimed in claim 1 in which the film coat comprises 5 to 15% by weight of the coated spheroids.

4. The composition claimed in claim 1 in which the ethylcellulose has a viscosity of 50 cps at 20° C.

5. The composition claimed in claim 1 in which the hydroxypropyl methylcellulose has a viscosity of 6 cps at 20° C.

6. The composition claimed in claim 1 in which the film coat comprises 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose.

7. The composition claimed in claim 1 in which the film coat contains up to 20% by weight of a plasticizer.

8. The composition claimed in claim 1 which contains 100 to 200 mg. of propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

9. The composition claimed in claim 1 in which, prior to coating, the spheroids contain 60% by weight of propranolol hydrochloride in admixture with 40% by weight of non-water-swellable microcrystalline cellulose, and the spheroids have a film coat consisting of 90% by weight of ethylcellulose having a viscosity of 50 cps at 20° C. and 10% by weight of hydroxypropyl methylcellulose having a viscosity of 6 cps at 20° C., the film coat comprising 9 to 10% by weight of the coated spheroids, and the said composition containing 160 mg. of propranolol hydrochloride.

* * * * *

EXHIBIT I

JC548 U.S. PTO 09/488629 01/20/00

Class	Subclass	ISSUE CLASSIFICATION
424	461	

PATENT NUMBER 6274171 6274171

U.S. UTILITY Patent Application

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/488629	D	424	461	1615	SPEAR

O.I.P.E. EXAMINER Q.A. UTP

PATENT DATE AUG 14 2001

APPLICANTS Deborah Sherman, John Clark, John Lamer 08/964,328

TITLE Extended release formulation

PTO-2040 12/99

ISSUING CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS
424	461

INTERNATIONAL CLASSIFICATION
A61K 9/52
A61K 9/54
A61K 9/62

CROSS REFERENCE(S) CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
424	457	458	459			
514	781	962				

☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER

☐ The term of this patent subsequent to _____ (date) if has been disclaimed.

☐ The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____

☐ The terminal ____months of this patent have been disclaimed.

DRAWINGS Sheets Drwg.	Figs. Drwg.	Print Fig.
0	0	0

CLAIMS ALLOWED Total Claims	Print.Claim for O.G.
25	1

(Assistant Examiner) (Date)

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

James M. Spear 5-7-01
(Primary Examiner) (Date)

(Legal Instruments Examiner) (Date)

NOTICE OF ALLOWANCE MAILED 5/09/01

ISSUE FEE

Amount Due	Date Paid
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PATENT APPLICATION

09488629

jc542 U.S. PTO
09/488629
01/20/00

FEB 16 0035
INITIALS ________

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/488,629	01/20/00	SHERMAN D	AHP-95011-P2

HM12/0104

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Patent Law Department 2B
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EXAMINER	
SPEAR, J	
ART UNIT	PAPER NUMBER
1615	4

DATE MAILED: 01/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95) 1- File Copy

Office Action Summary	Application No. 09/488,629	Applicant(s) SHERMAN, ET AL.
	Examiner JAMES M. SPEAR	Group Art Unit 1615

☒ Responsive to communication(s) filed on *Jan 20, 2000*

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-22* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *21 and 22* is/are allowed.

☒ Claim(s) *1, 12, 18, and 19* is/are rejected.

☒ Claim(s) *2-11, 13-17, and 20* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2,5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 18 and 19 contain the trademark/trade name HYDROXYPROPYLMETHYLCELLULOSE TYPE 2208 and TYPE 2910 and ETHYLCELLULOSE TYPE HG 2834. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to

identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a hydroxyalkylcellulose (hydroxypropylmethylcellulose) and ethylcellulose and, accordingly, the identification/description is indefinite. It is unclear as to what the type terminology is indicative of and how the various compounds differ based on the number notation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al U.S. 4,138,475 in view of Wong et al U.S. 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to formulate the core spheroid. See Abstract, example and claim 1. The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art.

Given the teachings of the prior art it would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in a sustained release dosage form to increase patient compliance when the need arises to administer both drugs. The motivation being a desire to obtain optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required.

Claims 2-11, 13-17 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 1, 12, 18 and 19 are rejected.

Claims 21 and 22 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308-2457. The examiner can normally be reached on Monday thru Friday from 6:30 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for this Group is (703) 305-3592 or 308-4556.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**thurman.page@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

James M. Spear

January 3, 2001

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

ATTACHMENT TO AND MODIFICATION OF NOTICE OF ALLOWABILITY (PTO-37)

(November, 2000)

NO EXTENSIONS OF TIME ARE PERMITTED TO FILE CORRECTED OR FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION, notwithstanding any indication to the contrary in the attached Notice of Allowability (PTO-37).

If the following language appears on the attached Notice of Allowability, the portion lined through below is of no force and effect and is to be ignored[1]:

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to comply will result in ABANDONMENT of this application. ~~Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).~~

Similar language appearing in any attachments to the Notice of Allowability, such as in an Examiner's Amendment/Comment or in a Notice of Draftperson's Patent Drawing Review, PTO-948, is also to be ignored.

---

[1] The language which is crossed out is contrary to amended 37 CFR 1.85(c) and 1.136. See *"Changes to Implement the Patent Business Goals"*, 65 *Fed. Reg.* 54603, 54629, 54641, 54670, 54674 (September 8, 2000), 1238 *Off. Gaz. Pat. Office* 77, 99, 110, 135, 139 (September 19, 2000).

Notice of References Cited

Application No.	Applicant(s)		
09/488,629	SHERMAN, ET AL.		
Examiner	Group Art Unit	Page 1 of 1	
JAMES M. SPEAR	1615		

U.S. PATENT DOCUMENTS

		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
	A	4,138,475	2/1979	McAinsh, et al	424	19
	B	5,552,429	9/1996	WONG, ET AL.	514	415
	C					
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FOREIGN PATENT DOCUMENTS

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Judith A. Johnston
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OIPE JC55 FEB 16 2001 PATENT & TRADEMARK OFFICE

AHP-95011-P2
PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman
John C. Clark
John U. Lamer

Serial No.: 09/488,629 Confirmation No.: 4728

Filed: January 20, 2000 Examiner: J. Spear

For: Extended Release Formulation Group: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

6/A Supp 3-5-01

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

Sir:

This is in response to the Office Action issued in connection with this case. The Office Action has been carefully reviewed and the following response prepared. Please amend the application as follows:

In the Claims:

Please cancel Claim 1.

2 Please amend the claims as follows: 2

1/2. An extended release formulation [according to Claim 1] of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule [wherein the] containing spheroids [are] comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

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02 FC:103 54.00 CH

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A

12. (Amended) An extended release formulation according to Claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose [2208], and about 62% by weight of microcrystalline cellulose.

17. (Amended) [A film coating composition] An extended release formulation according to Claim 2 wherein the film coating composition is [which is] comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0 - 51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. (Amended) [A film coating composition] An extended release formulation according to Claim 2 [which] wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution, [type HG 2834] and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12% [type 2910].

19. (Amended) An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose [type 2208], coated with a quantity of a mixture comprised of 85% ethyl cellulose [type HG 2834] and 15% hydroxypropylmethylcellulose [type 2910] sufficient to give coated spheroids having a dissolution profile [which gives the desired release rate over a 24 hour period] in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time	Average % Venlafaxine HCl Released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

In Claims 3, 4, 6 and 11, please delete "Claim 1" and insert --Claim 2-- therefor.
In Claim 8, please delete "Claim 6" and insert --Claim 2-- therefor.
In Claims 13, 14, 15, and 16, please delete "A composition" and insert --An extended release formulation-- therefor.

Please add the following new claims:

~~22~~ 23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23 ~~24~~. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24 ~~25~~. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25 ~~26~~. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses o venlafaxine hydrochloride which comprises administering orally to a patient in need

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thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Remarks

Claims 1-22 were pending in this case. Applicants appreciate the Examiner's indication that Claims 21 and 22 are allowed and that Claims 2-11, 13-17 and 20 are allowable. Claims 1, 12, 18 and 19 were rejected. Claim 1 was cancelled by this paper, without prejudice to its presentation in a divisional application. Claim 2 was rewritten in independent form by incorporating the subject matter of Claim 1. Claims 3, 4, 6 and 11 were amended to depend from Claim 2 rather than from cancelled Claim 1. Claims 12, 18 and 19 were amended to delete reference to trademarks/-tradenames. Claim 19 was also amended to specifically enumerate the dissolution profile referenced in the claim. Claims 13-18 were amended to proper dependen form by conforming their preambles to that of Claim 2 from which Claims 13-18 depend. Claims 8-10 were amended to depend from Claim 2 rather than from Claim 6 (which depends from Claim 2). New Claims 23 through 26 were added. New Claims 23 through 26 are supported throughout the specification and particularly, for example, at page 3, lines 14-19. No change in claim scope is intended by these amendments.

Claims 12, 18 and 19 were rejected under 35 U.S.C. §112, second paragraph, because they recited trademarks or tradenames. Applicants have amended Claims 12, 18 and 19 to delete trademarks/names. Reference is made generically instead to hydroxypropylmethylcellulose or ethylcellulose as supported, for example, in Claim 2, and in the specification at Page 6, line 30 through Page 7, line 4. Claims 12, 18 and 19 should not be limited to the particular hydroxypropylmethylcellose or ethylcellulose identified by the trademark/name.

Claim 1 was rejected under 35 U.S.C. §103(a). Claim 1 was cancelled, without prejudice to its presentation in a divisional application. Accordingly, this rejection is moot.

Claims 2-11, 13-17 and 20 were objected to as being dependent upon a rejected base claim. Claim 2 has been rewritten as an independent claim. Claims 3-

11, 13-17 and 20 have been amended so that they depend, directly or indirectly, from allowable Claim 2. Accordingly, this objection should be withdrawn.

In view of the foregoing, Claims 2-26 are in condition ready for allowance. An early and favorable Notice of Allowance is respectfully requested.

Respectfully submitted,

Rebecca R. Barrett

Rebecca R. Barret
Reg. No. 35,152

Dated: February 16, 2001

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02-20-01

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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Judith A. Johnston
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Judith A. Johnston
(SIGNATURE OF PERSON MAILING PAPER OR FEE)

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Docket No. AHP-9311-PC
PATENT

OIPE JC55
FEB 16 2001
PATENT & TRADEMARK OFFICE

In re Patent Application of D.M.Sherman; J.C.Clark & J.U.Lamer

Serial No. 09/488,629 — Examiner J. Spear

Filed January 20, 2000 — Group 1615

For Extended Release Formulation — CONFIRMATION NO. 4728

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED							
	(1)	(2) CLAIMS REMAINING AFTER AMENDMENT	(3)	(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
	TOTAL CLAIMS	* 25	MINUS	** 22	3	x $18.	54.00
	INDEP. CLAIMS	* 9	MINUS	*** 6	3	x $80.	240.00
	MULTIPLE DEPENDENT CLAIMS	0		0	0	$270.	0.00
				TOTAL ADDITIONAL FEE FOR THIS AMENDMENT →			294.00

* If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

☐ Fee for Terminal Disclaimer under 37CFR 1.20 (d) ($110.00) is also transmitted herewith.

☐ Fee of $_____ pursuant to 37 CFR 1.17(a) for extension of time under 37 CFR 1.136(a) is also transmitted herewith.

☒ Charge $ 294.00 to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Rebecca R. Barrett

Rebecca R. Barrett
Reg. No. 35,152
February 16, 2001

FORM PO-1083 (11-89)

USCOMM-DC 80425-P89

M2769-1N (12/00)

EXHIBIT J

US006274171B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,274,171 B1**
(45) **Date of Patent: Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: **Deborah M. Sherman**, Plattsburgh; **John C. Clark**, Peru, both of NY (US); **John U. Lamer**, St. Albans, VT (US); **Steven A. White**, Champlain, NY (US)

(73) Assignee: **American Home Products Corporation**, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/488,629**

(22) Filed: **Jan. 20, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** **424/461**; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/495, 494, 424/461, 458, 459, 457, 456, 462

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,954,959		5/1976	Pedersen	424/21
4,138,475	*	2/1979	McAinsh et al.	424/19
4,369,172		1/1983	Schor et al.	424/19
4,389,393		6/1983	Schor et al.	424/19
4,535,186		8/1985	Husbands et al.	564/336
4,966,768		10/1990	Michelucci et al.	424/468
5,506,270		4/1996	Upton et al.	514/730
5,552,429	*	9/1996	Wong et al.	514/415

FOREIGN PATENT DOCUMENTS

0654264	11/1994	(EP) .
0667150	1/1995	(EP) .
0797991	10/1997	(EP) .
9427589	12/1994	(WO) .
9737640	10/1997	(WO) .

* cited by examiner

Primary Examiner—James M. Spear
(74) *Attorney, Agent, or Firm*—Rebecca R. Barrett

(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

25 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine Is hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about I percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\%\ \text{Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(Vl)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4. hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm×4.6 mm, 5 μ; column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by is weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6–8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0–51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0–51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0–51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.:

Time	Average % Venlafaxine HCl Released
2	<30
4	30–55
8	55–80
12	65–90
24	>80.

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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EXHIBIT K

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT L

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT M

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT N

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT O

EXHIBIT REDACTED IN ITS ENTIRETY